THE BRITISH JOURNAL

OF

DERMATOLOGY

APRIL 1953

BOSTON
NOV 2 1964
MEDICAL LIBRARY

A CLINICAL STUDY OF LEUKONYCHIA.*

J. C. MITCHELL.

CHANGES in the nails in general illness were described by Hippocrates (*circa* 400 B.C.), and by Reil of Halle in 1792 in *Memorabili Clinicorum Fasiculi Halae*. Reil gave a further description in his work on the Diagnosis and Treatment of Fevers in 1804.

In 1869 Samuel Wilks described furrows appearing on the nail of a patient after an attack of gout. He stated that he could find no previous description in the literature, but that Erasmus Wilson had drawn his attention to a publication by J. H. S. Beau in 1846. In 1870 Wilks described furrows in the nails in cases of diphtheria and acute rheumatism. He quoted Dr. Maclean of Colchester in naming the furrows "hunger traces"; Dr. Maclean had told him that similar furrows could be seen on the hooves of horses, and that indentations or traces appeared on the wing and tail feathers of domestic fowls and captive birds. Wilks likened the condition to the changes in the hair and teeth which might accompany general illness. He himself had these furrows and lines after illness, and wrote "My opinion is that the furrows and white lines on the nails show the mark of death or approaching death . . . if he, the patient should fortunately recover, the sign of death is written upon him."

The presence of white spots or streaks on the nails has been recognized for centuries (Frankus, 1646), and unrecorded observations may be presumed from the mystical and folk-lore names which such changes in the nail have received; these include "gift spots," "fortune spots," "lies," and "sweethearts." Other names given to the condition include canities unguium, albugo, flores unguium, achromia unguium, white spots, marble nails, *decolorization des ongles*, hunger traces, and anaemic streaks.

* A shortened version of an essay awarded the Paul Phillip Reitlinger Prize of the University of London.

The literature concerning leukonychia, in all its forms, is extensive. Leukonychia may be congenital: Pardo-Castello (1941) records a case in which congenital leukonychia was present in exactly half the nails of the great and second toes in a coloured man. Costa (1947) and Stubenbord (1935) recorded cases of congenital total leukonychia. Joachim (1936) recorded hereditary dystrophy of hair and nails in 6 generations. Samuel (1918) recorded familial melano-leukodermia with leukonychia.

Trauma is supposed to be the cause in many cases, producing small fractures in the cellular compact of the nail and permitting air to collect between the cells with the resulting white discoloration (Pardo-Castello, 1941). Manicuring excesses and repeated pressure on the free edge of the nail have been incriminated (Pardo-Castello, 1941). Netherton (1929) attributed leukonychia to manicuring with the orange stick, and stated that the appearance of new spots ceased after prohibition of manicuring. Sykes (1897) stated that in his own person he could produce white specks on the nails by scraping, pressing back and cutting the fold of the nail. Heidingsfeld (1900) described the cases of six young women all of whom manicured. Leukonychia was most marked on the right hand, that is, the hand most liable to injury by unskilled manipulation with the left hand. Unna (1896) stated that the punctate forms are caused, for the most part, by slight injuries to the nails most frequently by the use of sharp instruments in pushing back the posterior fold. Parkes Weber (1899) noted that his patients with leukonychia manicured, but he attributed the condition to the menstrual loss.

Singer (1931) found leukonychia present in 62% of 100 normal persons selected at random, being found in 58% of the men and 75% of the women.

Sabouraud (1922) believed that leukonychia occurred in weak, tired nervous persons, particularly in women, and that it is often an early sign of tuberculosis. Josephson and Lerner (1934) related leukonychia to upper respiratory tract infections, and claimed to prevent both by producing acidosis by the administration of ammonium chloride.

Eller and Anderson (1928) reported leukonychia totalis of all the fingernails in a patient suffering from neural leprosy. Pardo-Castello (1941) records a case of leukonychia totalis in a coloured patient suffering from leprosy. He states that diffusion of the lunula is a very common phenomenon in leprosy and in other dystrophic conditions of the extremities. The lunula loses its shape and the anterior limit spreads forward and seems to invade all the nail bed. This is due to formation in the nail-bed of a granular layer loaded with keratohyalin and finally results in defective cornification. It is thought that the white colour of the lunula is due to the fact that the nail cells have not become entirely cornified and still retain granules of keratohyalin. Nevertheless Burrows (1919), from his histological studies, concluded that the opacity of the lunula is not caused by any peculiarity of the structure of the nail or

of its matrix, but is the result of reflection of light at the junction of the matrix and the connective tissue of the nail bed. He states that the matrix and its underlying connective tissue are more loosely adherent at the lunula than elsewhere.

Heller (1927) attributed leukonychia to trophic nerve disturbances and Wilks (1870) noted it following gout, diphtheria, cholera and acute rheumatism. O'Donovan (1938) noted leukonychia totalis in a newsvendor and in a pork pickler and found arsenic, x-rays and ointments useless in treatment. Krantz (1932) noted transverse bands of the colour of the lunula in the finger-nails in thallium poisoning ; Adler (1932) noted leukonychia in thallium poisoning.

Aldrich (1904) described leukonychia striata transversus arsenicalis, and Parkes Weber (1918) attributed a case to arsenical poisoning. Woolf (1925) listed relapsing fever, typhoid fever, multiple peripheral neuritis, toxic gastro-enteritis, arsenical poisoning and frost-bite as causative. He had noted leukonychia after fractures of bones of a limb, and reported a case of chronic ulcerative colitis seen on the 67th day after ileostomy. The patient had gained 40 lb. in weight since operation. There was a white band on all the finger- and toe-nails corresponding to the date of the operation, and the distal part of the nail was thinner and pinker than the proximal part.

Alkiewicz (1947) described leukonychia in trichinosis, de Almeida (1945) attributed a case to administration of emetine, Urbach (1945) described a case following cardiac infarction, and Cook (1945) described exfoliative dermatitis due to sulphathiazole characterized by recurrent attacks with Beau's lines and alopecia. Banyai and Cadden (1944) described changes in the lunulas of the finger-nails in tuberculosis, and Spira (1943) described mottled nails as an early sign of fluorosis.

Leukonychia was classified by Unna (1896) as follows :

1. Leukonychia punctata where the predominating lesions are in the form of spots.
2. Leukonychia striata where they are in the form of bands or striae.
3. Leukonychia totalis where they involve the nail in its entirety.

Parkes Weber (1918) suggested a fourth group—incomplete or subtotal leukonychia. Unna (1896) designated all forms due to trauma or artificial causes as leukopathia unguium in contradistinction to leukonychia, which he reserves for the spontaneous or idiopathic forms. Joseph (1898) limited the use of the term leukonychia to the type totalis.

The Histology of Leukonychia.

Unna (1896) and Joseph (1898) carried out histological examination of affected portions of the nail, and stated that the white spots were due to the presence of air in and between the nail cells.

Heidingsfeld (1900) found that, microscopically, the affected portions of the nail showed a band of cells which retained their nuclei, stained deeply and preserved their original form, and ascribed these characters to a failure to undergo normal keratinization. These findings were confirmed by Sibley (1911), who softened the nail with nitric acid and stained with safranin. He found the affected nail to be occupied by nucleated imperfectly keratinized cells.

Becker (1930) found that the affected portion of the nail contained an abnormal stripe about mid-way between inner and outer surfaces. The cells were larger than normal, the nuclei more prominent and both nuclei and cells took only acid stains. In some portions keratohyalin granules were seen in cells immediately towards the surface from the stripe. No air was found in the nail. Singer (1931) pointed out that keratohyalin is much more soluble than keratin in strong nitric acid, and attributed Unna's findings to an error in technique.

Alkiewicz (1935) attributed the white colour of leuconychia to the presence of intracellular granules situated in the protoplasm of the cells. He stated that their true colour is yellow-brown but, by refraction, they give to the spots an ivory-white appearance comparable with the colour of an emulsion containing droplets of oil. They are not composed of keratin, he states, of fat, lime, cysteine or of any substance which usual stains can differentiate. These " corpuscles " are insoluble in alcohol, ether, anilin, benzol, strong acids and alkalis. They do not stain with any of the usual dyes but reduce silver salts and give a positive dopa reaction. They therefore seem to be " leucomelanine."

Thus it appears likely that leuconychial spots are produced by a local or general defect of normal keratinization of the nail plates. Parakeratosis of the skin is commonly accompanied by infiltration of air between the cells ; for instance, the silvery-white colour of psoriatic lesions is so caused. It is possible, therefore, that infiltration with air may play some part in the production of leuconychia. This view is supported by the findings of Brauns (1903) that microscopical examination of affected portions of the nail showed a parakeratosis together with the presence of air spaces between the cells which had dried up and shrivelled.

The Present Investigation.

It was decided that frequent and careful study of the nails of one apparently normal person might throw light on the natural history of leukonychial spots. The observer's nails were, therefore, inspected at a regular hour twice each day and the position of each leukonychial spot was recorded on nail charts daily for one year.

A nail chart in the form of a rubber stamp was made (Fig. 1) and ten charts were used for each day's record. It was found that leukonychial spots were seen to best advantage in bright sunlight but in the absence of this, illumination with a 210 v./100 w. electric light bulb was satisfactory. The observations were made by naked eye and confirmed in each case with a hand lens (magnification × 8).

During the observation period the observer enjoyed good general health. The haemoglobin was estimated as 105 per cent. (15·5 g.) on the first day. The blood Wassermann reaction was negative, and scrapings from the nails were negative for fungus on three occasions.

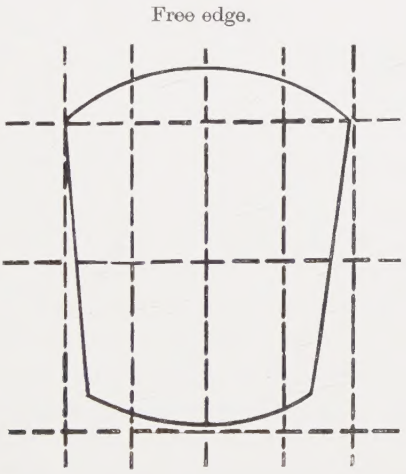

Fig. 1.

The nails were of a regular and comparable shape, corresponding fairly well to the schematic representation of the nail chart. Each nail exhibited a well-marked lunula measuring 0·1 to 0·2 cm. on each finger-nail and up to 0·4 cm. on each thumb-nail.

The nails were cut with spring nail clippers, leaving about 0·1 cm. free edge, and the cuticles were very gently pushed proximally once weekly.

The radial part of the nail of the right middle finger suffered daily superficial abrasions with pumice stone.

Each nail bore numerous faintly defined longitudinal striations, most marked on the thumb-nail. No transverse ridges nor furrows (Beau's lines) were present and there was no koilonychia. The nail of the left index finger bore about 9 circular depressions each less than 0·05 cm. diameter distributed evenly over its surface. These had been noticed for some years as a constant feature of this nail, being apparently formed regularly on the growing nail; they were not charted.

Results.

As shown in Table I, the complete history of 105 leukonychial spots was observed. Eighty-three of these appeared over the lunula and 22 appeared

Table I.

	Complete history observed.				Incomplete history observed.			
					Present at start of observation period.		Present at end of observation period.	
	Appeared over lunula.	Appeared on nail.	Cut off.	Disappeared.	Disappeared.	Cut off.	Appeared over lunula.	Appeared on nail.
Left little finger	10	2	8	4	—	12	—	1
Left ring finger	9	1	4	6	2	1	3	—
Left middle finger	4	1	2	3	1	—	1	1
Left index finger	7	1	—	8	1	—	—	—
Left thumb	—	—	—	—	—	—	—	—
Right little finger	12	6	11	7	—	4	—	—
Right ring finger	7	4	9	2	—	4	3	—
Right middle finger	12	2	7	7	—	2	1	—
Right index finger	11	4	6	9	1	1	1	—
Right thumb	11	1	8	4	6	—	1	—
Total	83	22	55	50	11	24	10	2

on the nail. Of these 105 spots, 55 grew out to the edge and were removed when the nails were cut, while 50 disappeared before they reached the free edge.

Forty-seven spots were observed during only part of their history. Thirty-five of these were present at the start of the observation period; of these 35 spots, 24 grew out and were cut off, and 11 disappeared before they reached the free edge. Twelve spots were present on the nails at the end of the observation period; of these, 10 had appeared over the lunula and 2 had appeared on the nail.

Adding these two sets of figures, we find that the fate of 152 spots was as follows: 79 spots grew to the free edge and were removed by cutting the nails, and 61 disappeared before they reached the free edge. The origin of 117 spots was that 93 appeared over the lunula and 24 appeared on the nail.

In addition to changes in position which occurred as the nails grew out, the leukonychial spots underwent other changes. As they appeared over the lunula they were ill-defined, white and semi-translucent; as they grew out in the visible nail, in the great majority of cases they became more clearly defined, more easily seen, a denser or more brilliant and shining white, and opaque. In many cases an ill-defined semi-translucent spot would fade in part leaving a dense speck or series of specks. Nearly all the alterations which occurred were of this nature, that is to say a fading or disappearance of a part

and an increase of white opacity of another part of a spot. Some semi-translucent and some opaque spots disappeared before reaching the free edge of the nail. Semi-translucent spots were more likely to fade before reaching the free edge, while opaque spots were more likely to survive and be removed by cutting, but in many cases opaque spots disappeared before reaching the free edge. Very few semi-translucent spots reached the free edge without becoming opaque. The disappearance of any spot was quite rapid, for a spot which had been growing out for 30, 40, or more days, unchanged, would start to fade and become invisible within a period of 10 days, or 7 days, and sometimes in a few days. Many semi-translucent spots disappeared within two or three weeks after appearing over the lunula, but once a spot had become opaque it usually survived over a month before disappearing. One opaque spot survived 80 days and disappeared 2 mm. from the free edge. It was found to be impossible to predict the fate of a spot ; some large opaque and apparently well-established spots disappeared, while small spots or specks survived to the free edge. Very few spots reached the free edge without becoming smaller.

Some spots increased in size. This increase in size took place when the spot was at least half-way to the free edge and, in two cases, took place when the spot was a few millimetres from the free edge and continued while the distal edge of the spot was continuous with the free edge of the nail. One spot survived at the free edge while spots which had appeared later advanced on it ; this suggests that the spot was increasing in size proximally. These points will be referred to in the discussion.

Those spots which appeared on the nail were of three varieties : Some of the 24 appeared a few millimetres distal to the lunula, and it is possible that they had, in fact, grown out over the lunula but had been invisible to the methods of examination used until they changed from semi-translucent to opaque. Other semi-translucent spots which appeared for the first time some way up the visible nail and which then underwent changes similar to those undergone by spots which had appeared over the lunula seemed to have been formed, without doubt, on the visible nail. The third variety of spot appeared nearly always at or near the free edge and was opaque from its first appearance.

It was found that there were certain inaccuracies in the method. Although the nail charts are of equal size, there was some inequality in size and variation in shape of the nails themselves ; there was some difficulty, therefore, in charting the altering positions of spots in the longitudinal axis. In retrospect it can be seen that it would have been better to have had four instead of three transverse lines on the stamp. Where there was irregularity or diffusion of the lunula, it was found very difficult to be exactly certain of the date of the first appearance of certain spots over the lunula.

Discussion.

There is conflicting evidence on the histological appearances of leukonychial spots, but the descriptions by Heidingsfeld (1900), Sibley (1911) and Becker (1930) and the microphotographs presented leave little reason to doubt that at least some leukonychial spots are areas of imperfect keratinization in which the cells retain nuclei and granules. These areas are therefore parakeratotic. The nature of the granules present in the nucleated nail cells has been assumed by these authors to be keratohyalin and the findings of Alkiewicz (1935) do not appear to prove that this is not the case. By analogy with parakeratosis in the epidermis, it is likely that these granules are keratohyalin or a substance intermediate between keratohyalin and keratin.

About one half of leukonychial spots disappear during their progress towards the free edge of the growing nail. It appears from the present study that parakeratotic cells can mature, lose keratohyalin, and form keratin up to 100 days after their formation. It seems that the chemical process of conversion of keratohyalin to keratin can occur in cells which have lost their blood supply several months previously.

It is usually stated (Pardo-Castello, 1941) that the nail is formed only at its proximal end, that is, at the matrix, and that the nail bed takes no part in its formation. The fact that leukonychial spots may appear for the first time distal to the lunula makes it very likely that the above view is wrong and that the cells of the nail bed are taking part in keratin formation, so that from time to time a group of cells is enclosed still nucleated in the nail plate. In support of this view is the work of Krantz (1932). He showed that if, after surgical removal of the nail plate, a mark is made on the nail bed, this mark grows out ahead of the new nail instead of being covered by it. Furthermore, when the nail plate becomes separated from its bed in pathological conditions, the epithelium acquires the property of producing corneous cells which, however, are not arranged to form a continuous layer but remain loose as " irregularly inspissated masses " (Pardo-Castello, 1941).

The next question to be considered is the increase in size of some leukonychial spots, for it is difficult to imagine that mature keratin should undergo a retrogressive change. These spots increased in size at or near the free edge where, if the nail bed is taking part in forming keratin, the spots are coming near the surface of the nail plate. It is likely that the spots would be nearing the surface also because at the distal end of the nail the superficial layers of the nail plate are being worn away by friction. It is possible, then, that there could be from friction or trauma a fracture of the nail plate over the leukonychial spot so that air enters between the shrivelled parakeratotic cells, and by extension of air between the layers of the nail the spot would actually increase in size. Now it can easily be shown that it is only necessary to introduce air

into the nail plate to produce a white spot. If the normal nail is scraped with a scalpel a fine white dust is produced ; this dust is whiter than a nail clipping, presumably because it is more refractive to light. The area on the nail which has been scraped is also white because it refracts light, but if the area is now moistened the whiteness disappears, because water has altered the refractive properties. It is suggested therefore that some leukonychial spots may be partly or entirely the result of introduction of air between cells of the nail plate, and that Unna's observation of 1896 may have been correct as far as the spots he was examining were concerned.

Some evidence about the aetiology of leukonychia has appeared from this control period. 152 leukonychial spots were observed during the growth of the equivalent of 40 new nails and no illness, at any rate of severity requiring confinement to bed, can be held responsible for them. Furthermore, at no time was a leukonychial spot observed on the toe-nails, which were inspected about once a week. It was noted that there was a tendency for leukonychial spots to be arranged in lines up the nail as if certain areas of the nail matrix had difficulty in maturing keratin and tended to throw off parakeratotic cells. It is difficult to believe that the haphazard injuries of unskilled manicuring could be responsible for recurrent trauma at one site and rarely at others, and during this observation period the observer pushed back the cuticles very gently.

One spot which developed on the nail was preceded 3 days before by a blunt injury at the same site ; this was a large and clearly defined spot, and it is unlikely that the nail bed could have produced it in so short a time. At other times several of the nails received multiple superficial abrasions, but no leukonychial spot could be attributed to these injuries. One further piece of evidence was obtained on this point : It was thought that, if the spots were due to trauma, they would be uncommon in the newly born ; the finger-nails of 65 babies were examined during the first week after birth and no leukonychial spots were observed in any case. On the other hand, it is quite common to see leukonychia striata on the nails of babies within the first three months of birth and these lines usually correspond to the date of birth.

Imperfect cornification or parakeratosis is a prominent pathological process in many skin conditions. In the nail a leukonychial spot represents an area of parakeratosis surrounded by mature keratin so that any experiment on the spot is well controlled. It might be possible, in further study, to examine the effects of various chemical substances in preventing or accelerating the conversion of keratohyalin to keratin by direct application to these spots. For the present, the investigation is proceeding with vigorous manicuring of the nail folds of the left hand with an orange stick while the right hand is not manicured, to determine the effects of this toilet in the production of leukonychial spots.

Summary.

The natural history of leukonychial spots was investigated by daily study and charting for one year.

References.

Adler, A. (1932) *Derm. Z.*, **63**, 259.
Aldrich, C. J. (1904) *Amer. J. med. Sci.*, **127**, 702.
Alkiewicz, J. (1935) *Przegl. derm.*, **30**, 109. Abstr. (1936) *Ann. Derm. Syph., Paris*, **7** sér., **7**, 99.
——— (1947) *Pol. med. Wkly.*, **2**, 1200.
Almeida, Jr., N. de (1945) *Hospital, Rio de J.*, **28**, 67.
Banyai, A. L., and Cadden, A. V. (1944) *Urol. cutan. Rev.*, **48**, 330.
Beau, J. H. S. (1846) *Arch. gén. Méd.*, **2**, 134.
Becker, S. W. (1930) *Arch. Derm. Syph., Chicago*, **21**, 957.
Brauns, T. (1903) *Arch. Derm. Syph., Wien*, **67**, 63.
Burrows, M. T. (1919) *Johns Hopk. Hosp. Rep.*, **18**, 357.
Cook, M. J. (1945) *Arch. Derm. Syph., Chicago*, **51**, 305.
Costa, O. G. (1947) *Ann. bras. Derm. Sif.*, **22**, 147.
Eller, J. J., and Anderson, N. P. (1928) *Med. J. Rec.*, **127**, 318.
Frankus, G. F. (1646) De Frankenau, *Onychologia curiosa sive de unguibus. Kenae.* Cited by Heidingsfeld, M. L. (1900) *J. cutan. Dis.*, **18**, 490.
Heidingsfeld, M. L. (1900) *Ibid.*, **18**, 490.
Heller, J. (1927) *Die Krankheiten der Nägel.* Zweite Auflage. *In* Jadassohn, J., *Handbuch der Haut- und Geschlechtskrankheiten*, 13/2. Berlin: Julius Springer. Cited by *British Encyclopaedia of Medical Practice* (1938). London: Butterworth and Co. (Publishers), Ltd., **9**, 85.
Joachim, H. (1936) *Ann. intern. Med.*, **10**, 400.
Joseph, M. (1898) *Derm. Z.* Cited by Heidingsfeld, M. L. (1900) *J. cutan. Dis.*, **18**, 490.
Josephson, E. M., and Lerner, C. (1934) *Arch. Derm. Syph., Chicago*, **29**, 703.
Krantz, W. (1932) *Derm. Z.*, **64**, 239. Abstr. (1933) *Arch. Derm. Syph., Chicago*, **28**, 408.
Netherton, E. W. (1929) *J. Amer. med. Ass.*, **93**, 116.
O'Donovan, W. J. (1938) *Practitioner*, **141**, 177.
Pardo-Castello, V. (1941) *Diseases of the Nails.* 2nd ed. Springfield, Illinois: Charles C. Thomas.
Reil, J. C. (1804) *Ueber die Erkenntnis und Cur der Fieber*, **2**, 113. Halle: Curt.
Sabouraud, R. (1922) *Entretiens dermatologiques*, n.s. **1**, 191. Paris: Masson et Cie.
Samuel, H. C. (1918) *Proc. R. Soc. Med.* (*Sect. Derm.*), **12**, 27.
Sibley, W. K. (1911) *Brit. J. Derm. Syph.*, **23**, 281.
Singer, P. L. (1931) *Arch. Derm. Syph., Chicago*, **24**, 112.
Spira, L. (1943) *J. Hyg., Camb.*, **43**, 69.
Stubenbord, J. G. (1935) *Arch. Derm. Syph., Chicago*, **32**, 761.
Sykes, W. (1897) *Brit. med. J.*, **2**, 1260.
Unna, P. G. (1896) *The Histopathology of the Diseases of the Skin.* Trans. Norman Walker. Edinburgh: W. F. Clay.
Urbach, E. (1945) *Arch. Derm. Syph., Chicago*, **52**, 106.
Weber, F. Parkes (1899) *Brit. J. Derm. Syph.*, **11**, 120.
——— (1918) *Int. Clin.*, 28th series, **1**, 108.
Wilks, S. (1869) *Lancet*, **1**, 66.
——— (1870) *Ibid.*, **1**, 3.
Wilson, E. (1869) *Ibid.*, **1**, 364.
Woolf, M. S. (1925) *Arch. Derm. Syph., Chicago*, **12**, 520.

AN INVESTIGATION INTO THE VALUE OF D,L-ALPHA—TOCOPHERYL ACETATE (VITAMIN E) IN THE TREATMENT OF GRAVITATIONAL ULCERS.

MAURICE LEE, F.R.C.S.
From the Varicose Vein Clinic, Prince of Wales's Hospital, London.

The treatment of gravitational ulcers of the leg with vitamin E, in the form of wheat germ oil, was first reported by Leranth and Frank as long ago as 1936. The subject did not, however, arouse general interest until Shute *et al.*, in 1948, noted improvement in sclerotic ulcers of the leg in patients under treatment with vitamin E for heart disease. Soon afterwards Burgess and Pritchard (1948*a*) reported improvement in sclerotic ulcers of the leg in patients on vitamin E, and Won Chia (1949), treating a series of 22 patients with post-thrombotic ulcers, achieved complete healing in all cases. Since that time several papers have been published on the subject, some reporting positive and others negative results. Successful results were reported by Burgess and Pritchard (1948*b*), Castagno and Impallomeni (1948), Vogelsang *et al.* (1948), Siedentopf and Kruger (1949), and Stritzler (1949). On the other hand, Pennock (1949) found that, in his series, vitamin E failed to hasten the healing time of leg ulcers. Having under my care a large varicose ulcer clinic consisting of out-patients with ulcers of many years' standing and frequently most intractable to conservative treatment, I decided that it would be interesting to attempt to evaluate earlier work on the use of vitamin E by carrying out a carefully controlled " blind " trial.

Scope of the Present Trial.

In order to pair the patients as accurately as possible they were divided into five groups, based solely on the clinical appearance of the ulcers. This method of grouping was purely arbitrary, and was merely intended to ensure that ulcers of similar sizes and appearance appeared in approximately equal numbers in the " treated " and " control " groups. Later, on analysing the results, it appeared that it might have been more helpful to have subdivided the patients on the grounds of aetiology, but this was not apparent when the trial was first started. The five groups were classified as follows :

I. Large superficial ulcers.
II. Small punched-out ulcers over the malleolus, usually associated with varicose veins.
III. Ulcers associated with brawny induration and oedema.

IV. Small multiple ulcers associated with eczema.

V. Miscellaneous ulcers which did not enter any of the above categories.

For each of these groups the Statistical Research Unit of the Medical Research Council provided a set of sealed envelopes, containing instructions to the pharmacist as to whether the patient was to be treated with vitamin E or with dummy tablets. Once it had been decided to which of the five groups above the patient belonged, he or she was given an envelope from that group and was instructed to take it to the pharmacist, the number of the patient's envelope being entered in the clinical notes. Thus, until the end of the trial, I did not know which patients were on vitamin E and which were controls.

The present series consisted of 57 patients who were under treatment for at least three months; 54 of them were in the series for six months or longer. Six other patients who had not, at the times of analysis, concluded three months' treatment were excluded, as were also three other cases (two on vitamin E and one on dummy tablets). Of these three patients, one did not return after the first visit, and a second admitted that she had not taken the tablets. In the third case it was accidentally discovered, immediately treatment started, that the patient was on dummy tablets; for this reason it seemed fairer to exclude him from the trial. There were 55 women and two men; ages ranged from 35 to 77 years, the average age for the whole series being 58·6 years.

No patient was included in the series who did not have a past history of at least two years' ulceration, the present ulcer being of at least six months' duration without obvious improvement. In many patients there was a history of recurrent ulceration over 20–30 years, and some ulcers had remained open without improvement for several years. When a patient was admitted to the series, it was first decided to which of the five groups he or she belonged. A very detailed history was then taken, especially with reference to a past history of deep venous thrombosis, of fracture or severe injury to the leg, or a long-standing history of varicose veins. Note was made of the presence or absence of oedema, of varicose veins, eczema, induration and the dorsalis pedis pulse.

At the first visit, the ulcer was carefully traced through transparent printer's paper, the drawing being transferred to graph paper. Similar drawings were made as regularly as possible at four-weekly intervals throughout treatment; by this means the area of ulceration could be measured on each occasion and the rate of healing calculated. In each case, the date on which healing took place was noted. In a number of patients, venous blood samples were taken before treatment and, as far as possible, at four-weekly intervals throughout treatment, the samples being submitted to the Dunn Nutritional Laboratory, Cambridge, for estimation of the tocopherol levels.

In addition to treatment with vitamin E or dummy tablets, vigorous local treatment was applied. Early in the trial, material from the ulcer bed was cultured in each case and one or more of the following organisms were almost always present: *Proteus*, *Ps. aeruginosa*, non-haemolytic streptococcus, *Staph. aureus*, and occasionally coliform bacilli. Attempts were made to sterilize the ulcer by the local application of preparations which are specific against these organisms. On the first visit in every case a streptomycin pack was applied to the ulcer; on subsequent visits, if the ulcer were still heavily infected, dressings such as B.M.H. gauze, Urosulphonet gauze or P.P.C. cream were applied and, in patients with marked eczema, bandages impregnated with coal-tar paste were frequently used. It was finally decided, however, that the presence of infection in an ulcer has little effect in delaying healing. Finally, adhesive bandages were firmly applied. For the first few weeks dressings were re-applied at weekly intervals; once marked improvement took place, bandages were changed only at 2–3 weekly intervals.

Vitamin E was given in the form of "Ephynal," a preparation containing synthetic d, l-alpha-tocopheryl acetate. The dose was 400 mg. daily, taken as four equally-divided doses after meals. Control patients were given dummy tablets of identical appearance. Full dosage was continued for 1–2 months after healing took place; the dose was then reduced to 200 mg. daily for a further 2–3 months. There were no side effects which could be attributed to the vitamin E and in no case was it necessary to reduce the dose.

Results.

In stating the results of treatment "complete healing" means that all ulcers had closed completely. Thus, in cases with multiple ulcers on one leg, or with both legs affected, the healing time was taken as the time when *all* ulcers had healed. When dealing with the healing *rate*, the "area of ulceration" means the total area of all ulcers in patients who had more than one.

All patients were observed for a minimum of 14 weeks and a maximum of 36 weeks. After 36 weeks a patient who was not completely healed was counted as a "failure" even if the ulcers were almost healed and later did heal completely. At 36 weeks such a patient was removed from the series and treated by any means considered desirable.

The 57 patients in the series were found to be distributed as follows:

Treatment.	Group I.	Group II.	Group III.	Group IV.	Group V.	Total.
Vitamin E	2	12	11	1	2	28
Dummy tablets	1	10	14	3	1	29
Total	3	22	25	4	3	57

Analysis of the drawings of the ulcer areas made at regular intervals gave the following results :

(a) *Frequency of Healing and Healing Time.*

Patients on vitamin E : 23 out of the 28 patients (82%) reached complete healing, the length of time varying from 4 to 31 weeks, with an average time of 11·3 weeks. 2 patients were failures, and 3 were still unhealed after 14, 15 and 22 weeks respectively.

Patients on dummy tablets : 24 out of the 29 patients (83%) reached complete healing, the time varying from 2 to 32 weeks, with an average of 14·6 weeks. Four patients were failures and one still unhealed at 22 weeks.

The difference between the average times required for healing (3·3 weeks) is not statistically significant. ($t = 1{\cdot}35$; $0{\cdot}2 > p > 0{\cdot}1$)

(b) *Healing Rate* (calculated as the percentage reduction at given intervals in the initial area of ulceration).

Duration of treatment.	Average percentage reduction. Vitamin E.		Dummy tablets.		Difference and test of significance.
4 weeks . . .	58·3	(24)*	45·1	(25)	+ 13·2% ($t = 1{\cdot}27$, $0{\cdot}3 > p > 0{\cdot}2$)
8 „ . . .	77·0	(27)	70·6	(24)	+ 6·4% ($t = 0{\cdot}73$, $0{\cdot}5 > p > 0{\cdot}4$)
3 months . . .	81·0	(28)	83·8	(29)	− 2·8% ($t = 0{\cdot}34$, $0{\cdot}8 > p > 0{\cdot}7$)

* Number of observations available in brackets.

A comparison of the healing rate was also made separately for Groups II and III, the only groups large enough to allow such comparison. The results for Group II followed much the same pattern as those for the whole series ; the average percentage reductions for the E and D groups at 4, 8 and 13 weeks were respectively 62 and 45, 87 and 82, 86 and 83. Group III showed a somewhat greater advantage for vitamin E, especially at 4 weeks, when the average percentage reduction was 68% compared with 40% for the patients on dummy tablets ($t = 2{\cdot}11$, $p = {\cdot}05$). The difference was less at 8 weeks (71 to 58%), and at 3 months had almost disappeared (83 to 79%).

(c) *Relapse Rate.*

Of the 47 patients whose ulcers had completely healed, 46 were followed up for periods varying from 1 to 79 weeks.

Vitamin E patients : The total follow-up period for the 23 healed patients amounted to 741 weeks, an average of 32 weeks. There were eight relapses

occurring in four patients. (Two further patients developed an ulcer on the leg not originally affected.)

Dummy tablet patients : The 24 healed patients had a total follow-up period of 710 weeks, an average of 30 weeks. There were 8 relapses in 7 patients.

There is clearly no difference whatever in the proportion of patients whose ulcers healed completely and little, if any, in the incidence of subsequent relapse. There was, however, an indication that the ulcers of patients on vitamin E had healed slightly more rapidly, particularly in Group III. It seemed worth while therefore to re-examine the case-sheets to find out if there were any type of varicose ulcer that appeared to benefit particularly from vitamin E therapy. It was noted that Group III, which showed the greatest difference between vitamin E and dummy tablets, was largely, but not entirely, composed of patients with a history of deep venous thrombosis prior to ulceration. For this reason the whole series of patients was re-grouped on the following basis :

Group A. Patients with a definite history of post-partum or post-operative thrombosis, or with a history of a fracture of, or severe injury to, the affected leg, occurring prior to ulceration.

Group B.—Patients with no history of thrombosis. Many, but not all, had marked varicose veins.

This division is open to criticism, since when it was made, the trial was no longer "blind." However, the previous careful history-taking made selection easy and, I believe, unbiased. In order to include as many data as possible in the regrouping, readings were this time included for patients who had attended for examination one week earlier or later than after the correct periods of 4, 8 or 12 weeks. In these cases an allowance was added to or deducted from the observed area of ulceration to give the area which would have been expected if the patients had attended at the right time. These corrections were small, and affected only 14 readings out of a total of 171. This procedure accounts for the different numbers of total readings before and after regrouping. The new grouping gave the following results :

Group A.

(a) *Frequency of Healing and Healing Time.*

Patients on vitamin E : 12 out of 14 patients (86%) who had completed 3 months' treatment healed in an average of 9·9 weeks. One patient was a failure, and one was still unhealed at 14 weeks.

Patients on dummy tablets : 9 out of 12 patients (75%) healed in an average of 15·8 weeks. Two patients were failures, and one was still unhealed at 22 weeks. The difference in average time required for healing was therefore 5·9 weeks. ($t = 1{\cdot}84$, $p = 0{\cdot}08$).

(b) *Healing Rate.*

Duration of treatment.	Average percentage reduction. Vitamin E.		Dummy tablets.		Difference.
4 weeks . . .	65·1	(14)*	35·6	(12)	+ 29·5% ($t = 2·45$, $p = 0·022$)
8 „ . . .	83·4	(14)	67·4	(12)	+ 16·0% ($t = 0·489$, $0·6 > p > 0·7$)
3 months . . .	89·2	(14)	79·8	(12)	+ 9·4% ($t = 1·10$, $0·2 > p > 0·3$)

* Number of observations available in brackets.

(c) *Relapse Rate.*

Vitamin E : 1 out of 12 patients. In one other patient an ulcer occurred on the opposite leg.

Dummy tablets : 4 out of 9 patients.

There was, it will be seen, a rather higher rate of healing, particularly in the first four weeks, in the group on vitamin E.

Group B.

(a) *Frequency of Healing and Healing Time.*

Patients on vitamin E : 11 out of 14 patients (79%) who had completed 3 months' treatment healed in an average of 12·9 weeks. One patient was a failure, and two were still unhealed at 14 and 15 weeks.

Patients on dummy tablets : 15 out of 17 patients (88%) healed in an average of 14·3 weeks. Two patients were failures.

The difference in average time required for healing was therefore 1·4 weeks ($t = 0·376$, $p = 0·7$).

(b) *Healing Rate*

Duration of treatment.	Average percentage reduction. Vitamin E.		Dummy tablets.		Difference and test of significance.
4 weeks . . .	47·8	(14)*	58·7	(17)	− 10·9% ($t = 0·927$, $0·4 > p > 0·3$)
8 „ . . .	69·7	(14)	73·6	(17)	− 3·9% ($t = 0·471$, $0·7 > p > 0·6$)
3 months . . .	76·8	(14)	87·6	(17)	− 10·8% ($t = 0·269$, $p = 0·8$)

* Number of observations available in brackets.

(c) *Relapse Rate.*

Vitamin E : 3 out of 11 patients. In one other patient, an ulcer occurred on the opposite leg.

Dummy tablets : 3 out of 15 patients.

In this group the patients on the dummy tablets fared rather better though the differences are not significant.

Biochemical Results.

Specimens of blood plasma were taken in many of the patients before dosing and at various intervals after dosing. Vitamin E, estimated by the ferric chloride method, in the patients who were given dummy tablets averaged 1·20 mg. per 100 ml. before dosing (21 readings on 21 patients) and 1·35 mg. after dosing (35 readings on 20 patients). For the patients dosed with d, l-alpha-tocopheryl acetate the corresponding values were 1·13 (25 readings on 25 patients) and 2·05 mg. (41 readings on 22 patients).

One patient out of 21 given the placebo showed on one occasion an increase in the plasma tocopherol of an order which might have been expected for a patient dosed with tocopherol. Five out of 25 patients who were dosed with tocopherol failed to show the usual increase in the level in the plasma after treatment.

No correlation was observed between the rates of healing of the ulcers and the individual levels of tocopherol in the blood plasma before or after treatment.

Discussion.

In the above trial ulcers which had resisted conservative treatment for prolonged periods were nearly all healed in a further 3 or 4 months, irrespective of whether tocopherol had been administered or not. This general tendency towards healing may possibly be explained by more vigorous local treatment, particularly by insistence on firm and continuous support with carefully applied adhesive bandages. The same intensive local treatment was given to all the patients in both treated and control groups.

The possible beneficial effects of tocopherol had therefore to be observed in patients who, it appears, would in most cases have been healed even if vitamin E had not been given. Since there was no difference in the final conditions of the patients, and little, if any, in their subsequent relapse rate, the speed of healing with and without tocopherol had to be closely considered.

The greatest differences between dosed and control patients were seen after four weeks and, in the two largest groups of ulcers into which division was first made, the rate of healing was rather faster in the treated group than in the untreated (though the difference was in one group statistically not significant and in the other of doubtful significance). At later times, 8 and 13 weeks, the differences became less, and none was statistically significant. When the patients were differently grouped, according to whether or not they had a past history of deep venous thrombosis, there was a significant difference in the rate of healing at 4 weeks, between the dosed and control patients who had suffered from thrombosis. The treated patients showed a rather more rapid improvement.

Summary.

1. An attempt was made to evaluate the effect of vitamin E in the treatment of stasis ulcers of the leg. A " blind " controlled trial was carried out on 57 patients with intractable ulcers and a long history of ulceration.

2. The patients were first subdivided into five groups, depending entirely on clinical assessment of the size and type of ulcer involved. Patients in each group were randomly allocated to daily doses of either d, l-alpha-tocopheryl acetate or a placebo, in addition to local treatment along orthodox lines. The rates of healing were studied by periodical measurements of the areas of the ulcers and by noting the times necessary for complete healing.

3. In nearly all the patients, whether on vitamin E treatment or on the control, the ulcer was completely healed in 3 to 4 months. Healing was, however, somewhat more rapid in the patients dosed with vitamin E than in those untreated, though with the possible exception of one group the differences were not statistically significant.

4. Rearrangement of the groups according to whether or not the patients had a history of deep venous thrombosis prior to ulceration indicated a rather greater (and statistically significant) degree of healing after four weeks' treatment in the treated compared with the untreated patients in the post-thrombotic group. In the group in which thrombosis had not been involved no significant difference was observed between dosed and undosed patients. In the present series, patients with post-thrombotic ulcers comprised about 45% of the total number of patients.

5. Estimations of tocopherol were made in the blood plasma before administering tocopherol or placebos and at intervals throughout the trials. Substantial increases were usually found in the patients dosed with tocopherol. No side effects were observed.

6. It is suggested that vitamin E is worth trying as an ancillary to local therapy in patients with post-thrombotic ulcers.

Acknowledgments.

This trial was partly carried out with the aid of a grant from the Medical Research Council. I also wish to thank Dr. J. P. W. Hughes and Dr. J. T. Boyd of the Council's Statistical Research Unit for statistical analysis of the results and for much helpful advice, and Dr. T. Moore and Dr. I. M. Sharman of the Dunn Nutritional Laboratory for the biochemical investigations and for help in preparing the paper. Thanks are also due to Roche Products Ltd. for supplying part of the " Ephynal " used in the trial and to Dr. Margaret Briggs for practical assistance.

References.

Burgess, J. F. (1948) *Lancet*, **2**, 215.
Burgess, J. F., and Pritchard, J. E. (1948) *Canad. med. Ass. J.*, **59**, 242.
Castagna, R., and Impallomeni, G. (1948) *Boll. Soc. piemont. Chir.*, **18**, 156.
Leranth, G., and Frank, L. (1936) *Orv. Hétil.*, **80**, 778.
Pennock, L. L. (1949) *Ann. N. Y. Acad. Sci.*, **52**, 413.
Shute, E. V., Vogelsang, A. B., Skelton, F. R., and Shute, W. E. (1948) *Surg. Gynec. Obstet.*, **86**, 1.
Siedentopf, H., and Krüger, A. (1949) *Med. Klinik*, **44**, 1060.
Stritzler, C. (1949) *Ann. N. Y. Acad. Sci.*, **52**, 368.
Vogelsang, A., Shute, E., and Shute, W. (1948) *Med. Rec., N. Y.*, **161**, 83, 155.
Won Chia, J. L. (1949) Thesis, Lima.

KAPOSI'S VARICELLIFORM ERUPTION: DIRECT TRANSMISSION TO A NURSE.

J. R. SIMPSON, M.B., M.R.C.P.,
Royal Devon and Exeter Hospital.

Kaposi's (1895) description of this disease gave no hint that it was contagious or infectious.

Juliusberg (1898) described the fatal case of a child who had never been vaccinated and whose mother subsequently developed vesicular lesions on her upper eyelid. Lynch (1945) has suggested that the mother's eruption might have been herpes simplex and her disease causally related to that of her child.

During the last twenty years many case-histories have been published, and technical improvements in the identification of virus have made it clear that the disease can be caused by the virus of either vaccinia or herpes simplex. It is exceptional for it to appear on a healthy skin, and the commonest pre-existing dermatosis is atopic eczema.

A history of contact with either vaccinia or herpes simplex was obtained in the majority of cases published recently, but there are comparatively few accounts of Kaposi's varicelliform eruption (K.V.E.) being transmitted direct from one case to another, and few reports of skin lesions occurring among the nurses in attendance which even suggested this diagnosis.

McLachlan and Gillespie (1936) reported an epidemic involving sixteen cases in a children's skin ward. No attempt was made to isolate a virus, but only one of the children had been vaccinated. The authors noted that three nurses suffered from acute septic throats and one developed three large pustular bullae on the forearms. Barton and Brunsting (1944) observed that three of the nurses attending one of their cases, the cause of which was not determined, developed vesico-pustular lesions on the hands but had neither fever nor malaise. Cultures from their lesions grew *Staphylococcus aureus* but no virus was isolated. Examples of direct transmission of K.V.E. were reported by Nimpfer (1936), Strickler (1944), Whittle *et al.* (1950), and Sommerville, Napier and Dick (1951). In all there was clinical or laboratory evidence that the virus was that of vaccinia.

Leider described the cases of a brother and sister living in the same household, both adults with chronic atopic eczema, one of whom developed K.V.E. six days after the other. No virus was isolated and there was no history of contact with either vaccinia or herpes simplex, but the sister had shown an immune reaction to vaccination two years earlier. Even if it be accepted that

herpes virus was responsible in each case, the known variation in the incubation period of K.V.E. suggests the possibility that both patients derived the infection from the same unknown source. In this connection it may be recalled that McLachlan and Gillespie noted a variation in the incubation period from 8 to 18 days with an average of 12·5 days, and that in the epidemic of sixteen cases reported by Fries, Borne and Barnes (1948), which was due to vaccinia, the extreme limits were 5 to 19 days with an average of 10·6 days.

The first account of an epidemic of K.V.E. proved to be due to herpes simplex virus was given by Esser (1941). Of eight children with atopic eczema in one ward four developed K.V.E. As the date of onset in each case was not stated and the source of infection was unknown this cannot be cited as an example of direct transmission of the disease. Sims and French (1948) reported an outbreak of K.V.E. in a children's ward in which there was laboratory evidence of infection by herpes simplex virus in two of the four secondary cases, but investigations were negative in the primary case.

Bettley (1949) reported the case of a child aged eighteen months with infantile eczema and typical K.V.E., together with that of a nurse attending her, who developed typical herpes simplex on one finger which she had grazed on the child's cot. No virus was isolated from either patient or nurse at the time, but the child was vaccinated successfully soon afterwards and the nurse gave no history of having had herpes before. Subsequently the child had several recurrences of infantile eczema with widespread herpetic lesions superimposed. The nurse had one recurrence of herpes simplex on the same finger some weeks later. Herpes simplex virus was recovered from the lesions in each case during these later episodes.

I have been unable to find a published report of K.V.E. being transmitted, as such, direct from one case to another with proof that the virus of herpes simplex was responsible in each case; nor have I seen an unequivocal record of a nurse taking the disease from a patient. The following two case-histories provide an example of both these features:

Case 1.—A boy aged 11 months was admitted to a cubicle in the children's ward on 27 January 1952. He had had infantile eczema for two months and had not been vaccinated; during the second week in January his mother developed a cold sore on the lips. On 26 January he suddenly became ill, was irritable and drowsy and refused his food. On admission his temperature was 104·4° F., but otherwise his general condition evidently did not cause alarm.

When I first saw him on 29 January large areas on the peripheral parts of the face and forehead were superficially ulcerated, covered with sero-sanguineous crusts and bled readily when these were removed. On the backs of the hands and on the left antecubital fossa there were closely set round, yellow, umbilicated papules, some of which were haemorrhagic. The trunk was spared, but there were patches of eczema on the front of the knees and ankles. The cervical and left axillary lymph glands were enlarged and tender. A blood-count was reported as follows: Hb. 9·32 g.%, R.B.C. 3,400,000, W.B.C. 7200. Differential normal.

He was treated by local application twice daily of 0·15% Dibromopropamidine cream and aureomycin by mouth. The initial dose was 200 mg. daily and this was gradually increased, as his condition deteriorated, until 1 February, when he had gross abdominal tympanites and right basal pneumonia, and seemed moribund. He was then given aureomycin 400 mg. daily, Sulphatriad 1·0 g. daily and Distaquaine 50,000 units twice daily. His general condition improved slightly in the next three days but the temperature continued to swing between 101° and 105°, the areas of ulceration grew larger, and fresh papules kept appearing on all the eczematous sites. On 4 February he was also given chloramphenicol, 500 mg. daily. Within twenty-four hours the temperature began to fall abruptly to normal and the eruption ceased to extend. On 6 February all parenteral treatment was stopped except chloramphenicol, which was continued for another six days. His slow recovery was interrupted on 3 March by a relapse of fever (102°) and lymphadenitis. Chloramphenicol was resumed immediately and both fever and adenitis subsided within forty-eight hours. The crusts eventually separated, leaving no scarring, but when he was discharged on 11 March his eczema was beginning to recur. He has attended as an out-patient many times since then for this reason and was readmitted for a fortnight in July 1952.

Case 2.—The sister in charge of the Children's Ward, aged 27 years, had never had eczema, but was under my care for several months in 1949 for a stubborn patch of occupational dermatitis at the base of the right thumb. She made a complete recovery and had no further trouble until she noticed slight chapping in that area on 31 January 1952, four days after the admission of Case 1, whom she had handled frequently. She had been vaccinated successfully in 1945, but had never suffered from herpes simplex, although she had in the past nursed many patients who developed it in the course of their illness. She was not aware of any recent contact with herpes simplex except the mother of Case 1, whom she had interviewed but not touched. On 1 February a papule appeared in the chapped skin and the next day she felt ill and feverish, had regional lymphangitis and went to bed. On 3 February another lesion appeared on the right thumb.

On 5 February there was on the base of the right thenar eminence a slightly tender, round, firm, red papule, 1·2 cm. in diameter and projecting 4 mm. above the surrounding skin which showed a mild degree of eczema. The papule was surmounted by a vesicle 5 mm. in diameter which oozed blood and serum when the roof was removed. On the dorsum of the proximal phalanx of the right thumb was another firm, dome-shaped papule 4 mm. in diameter and of normal colour but with a red halo. There was axillary lymphadenitis but no fever.

No treatment was given except rest and inunction twice daily with 3% aureomycin cream. Her malaise continued for a week. The smaller lesion, which was not disturbed, showed slight umbilication before it became crusted and healed. On 14 February three more small papules, 2 mm. in diameter, appeared over the metacarpo-phalangeal joint of the right thumb. On 26 February all crusts had separated, leaving only faint erythema.

Laboratory Investigations.

Material was sent to the Virus Reference Laboratory, London, and the following reports were received :

29 February : Crusts were taken from Case 1. 10% membrane suspension produced focal lesions on chorio-allantois ; neutralized by positive herpes serum—herpes simplex.

Crusts from his mother's lip : No virus isolated.

Sample of his mother's serum : Neutralization test for herpes simplex– antibody present.

5 February: Fluid was taken from the vesicle in Case 2, and also the roof of the vesicle. Chorio-allantoic membrane inoculation—herpes simplex virus isolated.

Summary.

Two cases of K.V.E. are reported. The second patient nursed the first.

Herpes simplex was proved to be the cause in each case.

Treatment with aureomycin had no apparent effect on the course of the disease.

It gives me great pleasure to express my thanks to Dr. A. J. Daly, who gave invaluable help in the general management of Case 1, and to Dr. A. D. Macrae of the Virus Reference Laboratory for the viral investigations.

References.

Barton, R. L., and Brunsting, L. A. (1944) *Arch. Derm. Syph., Chicago*, **50**, 99.
Bettley, F. R. (1949) Annual Meeting, British Association of Dermatology, 1949 (unpublished).
Esser, M. (1941) *Ann. Paediatr., Basel*, **157**, 156.
Fries, J. H., Borne, S., and Barnes, H. L. (1948) *J. Pediat.*, **32**, 532.
Juliusberg, F. (1898) *Arch. Derm. Syph., Wien*, **46**, 21.
Kaposi, M. (1895) *Pathology and Treatment of Diseases of the Skin.* London: Baillière, Tindall & Cox, p. 346.
Leider, M. (1951) *Arch. Derm. Syph., Chicago*, **63**, 456.
Lynch, F. W. (1945) *Ibid.*, **51**, 129.
McLachlan, A. D., and Gillespie, M. (1936) *Brit. J. Derm.*, **48**, 337.
Nimpfer, T. (1936) *Arch. Derm. Syph., Wien*, **174**, 518.
Sims, E. B., and French, E. L. (1948) *Clin. Rep. Adelaide Child. Hosp.*, **1**, 99.
Sommerville, J., Napier, W., and Dick, A. (1951) *Brit. J. Derm.*, **63**, 203.
Strickler, A. (1944) *Urol. cutan. Rev.*, **48**, 340.
Whittle, C. H., Lyell, A., Miles, J. A. R., and Stoker, M. G. P. (1950) *Brit. J. Derm.*, **62**, 195.

CORRESPONDENCE

A LETTER FROM U.S.A.

(The Editor invited Dr. George C. Wells, Assistant Professor of Dermatology in the University of Chicago, to write a letter for publication in the Journal mentioning some aspects of dermatology in the United States which would be likely to interest readers. We are happy to present Dr. Wells's reply.)

SIR,

It would be out of place and indeed unkind to boast of things that are more plentiful here in America, but I really do feel that we have more fungi. At least mycoses are more to the fore here than in Europe, partly because superficial fungus infections are more prevalent, partly because the general public is more conscious of such matters, partly because there are some bizarre deep mycoses peculiar to this part of the world, partly because dermatologists in training here are very thoroughly instructed in all relevant aspects of mycology, and partly because the great pharmaceutical houses sponsor research in and clinical trials of anti-fungal agents with self-seeking generosity. I have chosen, then, to mention some trends in mycology, and must leave much unsaid of present interest here in other facets of dermatology. Firstly, one must allow that in spite of the alarming number of fungicidal remedies in general use and undergoing trial for superficial fungus infections, there has been no notable advance in therapy during the past few years since the recognition of the value of certain fatty acids, and one usually has to rely upon x-ray epilation for cure of *Microsporon audouini* infection of the scalp. You will recall that it is not many years since *M. audouini* was introduced into this country, and that epidemics swept the eastern seaboard, and the disease has now become endemic in many States. We are now being invaded from the opposite extreme, for, creeping over the border from Mexico into California, we have non-fluorescent endothrix scalp infection with *Trichophyton tonsurans*. A new approach to the management of trichophyton infection of nail-plates employs the hydrogen-bond-splitting effect of lithium bromide as used by the wool research chemists. The idea is interesting, but its clinical usefulness is uncertain.

Of late there has been great interest in the use of the aromatic diamidines in the treatment of some deep mycoses, and excellent results have been reported both in cutaneous and in systemic blastomycosis. These drugs are familiar to you in the treatment of kala azar and of trypanosomiasis, and propamidine has been used locally for infected burns and wounds. Two cases of skin infection with *Blastomyces dermatitidis* that I have seen treated with intravenous stilbamidine have responded very well indeed, and it should be men-

tioned that both these patients had had all manner of other treatments in vain. With stilbamidine the toxic dose is close to the therapeutic, and injections must be given with great care. Solutions should be made up just before they need to be used, as exposure to bright light renders them highly toxic and reduces their effectiveness. Immediate disasters have been largely eliminated by giving the drug in a slow intravenous drip of 5% glucose, but the possibility of toxic liver damage accruing over longer periods of treatment must not be forgotten. There is also a peculiar trigeminal neuropathy which often occurs several months after completion of the therapy. I understand that stilbamidine has been used successfully in cases of infection with *Paracoccidioides braziliensis*, *Sporotrichium schenkii*, and in some cases of actinomycosis and nocardiasis.

Before long more efficient agents may become available for the treatment of moniliasis, and perhaps of other superficial fungus infections. With the increasing use of antibiotics effective against bacteria but ineffective against yeasts and fungi, one is seeing more cases of disturbed mucosal flora and occasionally severe thrush. It is appropriate that the actinomycetes, close relatives of the bacteria, should provide a possible answer to this unfair discrimination against the bacteria. Of various cultures of actinomycetes isolated from soil, at least half have anti-fungal properties and some provide potent fungicidal and fungistatic antibiotics. Amongst these actidione, fradicin and fungiciden are active against yeasts and fungi, though they differ widely in their selectivity of action. For instance, actidione is effective largely against non-pathogenic organisms such as aspergillus and the cryptococci but does not inhibit the dermatophytes, so that it may be added to culture media as a kind of weed-killer. In this group of antibiotics there are some highly active against *Candida albicans*, and I understand that candicidin has got to the rabbit-saving stage and shows great promise.

There is some confusion in the literature between generalized moniliasis and acrodermatitis enteropathica of Danbolt. The latter appears to be a clinical entity, with moniliasis as a common secondary complication. I mention this rare and often fatal disease because of the dramatic cure of a child whose progress we have followed with great interest in our clinic. The disease seems to start when breast-feeding is stopped, and is manifested by:

(i) Gastro-intestinal disturbance (usually periodic diarrhoea, often with secondary moniliasis).

(ii) Vesicular eruptions around the body orifices and on the extremities (these lesions progress to crusting and scaling plaques and are prone to secondary infection with yeasts or cocci. Oral thrush may also be present).

(iii) Alopecia (usually total).

(iv) A peculiar head-hung misery (the child is fretful and withdrawn).

There are records of familial cases. Exacerbations of diarrhoea are usually accompanied by relapse of all the other symptoms, and it has been supposed that the essential disease is in the gastro-intestinal tract.

The little girl that I mentioned was $2\frac{1}{2}$ years old and the disease had been present since the age of 2 months. Various treatments had been in vain though hospital care had brought partial remissions and the moniliasis had been cleared up. The response to diodoquin was, however, immediate and the cure has apparently been complete. An account of this case has been written by Drs. C. J. Dillaha, A. L. Lorincz and O. R. Aavik, and is to appear in the *Journal of the American Medical Association*.

The pathogenesis of this disease is intriguing. As diodoquin is scarcely absorbed from the gut, its direct effect must be upon the gastro-intestinal tract or its contents; and whatever changes occur there are reflected in cessation of vesication in the skin, steady growth of hair and complete reversal of the depression and irritability. From some points of view it would be convenient to regard the remote manifestations as "id" reaction to intestinal moniliasis, but we were satisfied that *Candida albicans* was not consistently present while the disease was active; and anyhow the non-inflammatory hair loss could hardly be an allergic reaction in this sense, and furthermore the oidiomycin skin test was negative in this case. So although the nature of the cure supports Danbolt's theory of gastro-intestinal pathology, we still have no notion of what that primary defect may be. I might add that diodoquin was quite without effect on a case of true intractable moniliasis with granulomatous skin lesions.

It may be that acrodermatitis enteropathica is not quite as rare as it appears to be. Besides difficulty in distinguishing it from generalized moniliasis, it is clear that some cases have been confused with epidermolysis bullosa. And what of the case illustrated in Lewis and Hopper's *Introduction to Medical Mycology* under the title of moniliasis of generalized type? Note the recurrent impetiginous lesions of the face and the alopecia, and realize that this condition had been present since earliest childhood. Could this be a *forme fruste* of Danbolt's disease persisting into adult life? Well, the remarkable thing is that even at this late stage either the patient or one exactly like him has responded to treatment with diodoquin.

I am,

Yours, etc.,

George C. Wells.

Section of Dermatology,
Department of Medicine,
University of Chicago:
January 1953.

BOOK REVIEWS

Cosmetic Dermatology.*

For some years past, at the Hôpital Saint-Louis, the authors, under the direction of Dr. Tzanck, have conducted special out-patient sessions for the treatment of acne, angiomas, allergic dermatitis, and the like. The present volume is partly the result of this special experience.

The study of dermatology by regions or according to some fortuitous quality such as cosmetic significance results in a curious balance of emphasis. For example, the authors' researches on acne vulgaris and their progressive views naturally receive full attention, and indeed occupy fifty pages; it is strange to find epithelioma discussed in three pages, and lupus vulgaris and lupus erythematosus not mentioned at all. Again, in a work of this size, it is surprising for stellate angioma to be described without reference to familial hereditary haemorrhagic telangiectasia, and for xanthoma tuberosum to be treated without mention of the serious and grave consequences of hypercholesteraemia. For reasons of this sort this book has a patchiness, leaving many gaps which need to be filled in, On the other hand, the authors are, no doubt, correct in supposing that too many dermatologists are preoccupied with the pathology of skin disorders at the expense of the patient's desire for a really good cosmetic result.

A substantial part of the book is devoted to the care of the normal or nearly normal skin and hair. Dermatologists are often not prepared to advise patients on such matters, but even so must not remain unaware of the nature of the multiple treatments to which the female face is daily subjected. The nature of cosmetics and their possible harmful effects are here concisely described, and much information collected together which would otherwise be available only after a wide search through the literature.

This book, of a specialty within a specialty, will interest every practical dermatologist: it is thoroughly up-to-date, sane and sound, and full of valuable tips originating, clearly, from the authors' own practical experience. F. R. B.

On Naevi and Miscellaneous Subjects.†

Another collection of short essays and case notes by Dr. Parkes Weber will be welcomed by dermatologists, who, again, are well catered for. Five of the twelve sections deal directly with conditions seen in the skin department, ranging from a general consideration of naevi to sclerodactylia and calcinosis, Sjögren's disease, diffuse lymphangiectasis and prurigo nodularis. The latter, possibly, is not a happy diagnosis for Case V, but that renders the case all the more worthy of study.

Of the ostensibly subcutaneous topics, it is to be noted that the child suffering from relative macrosomia had an undiagnosed bullous eruption: that not a few of Osler's obscure diseases affect the skin: and that the remarkable examples of retrograde peristalsis and faecal vomiting in functional nervous conditions offer a new approach to the aetiology of Kyrle's disease.

---

* *Précis de Dermatologie Corrective*. By Edwin Sidi and R. Aron-Brunetiere. Paris, Masson et Cie, 1952. Pp. 578. Illus. 87. Price 3600 frs.; in clothboard 4200 frs.

† *On Naevi and Miscellaneous Subjects*. By F. Parkes Weber. London: H. K. Lewis & Co. Ltd., 1952. Pp. 72. Illus. 24. Price 12*s*. 6*d*.

Erudite, provocative and stimulating, this little book of 70 pages, excellently printed and well illustrated, is to be recommended to all interested in medicine in general and the skin in particular. P. B.

The Hair and Scalp: A Clinical Study.*

The fourth edition of this well-known work follows the same general plan as previous editions, but it has been carefully revised and in parts rewritten. New material has been added including five additional illustrations, but as a result of skilful condensation here and there the total bulk has been increased by only twelve pages. As in the third edition, the first four chapters deal with the structure and properties of hair, its care, and methods of waving and their hazards, but with a much more detailed account of the "cold wave." Greying of hair and the possible relation of vitamin B metabolism to this process is also discussed more fully. Some of Dr. Savill's views in this matter are of course controversial. The statement on p. 15, repeated from the third edition, that "adrenalin and its oxidation products seem to be the precursors of melanin" will not meet with general acceptance. She still regards the hair-shaft as a living tissue, apparently with justification, and advances further evidence of sudden changes of colour. Chapter IV, a fascinating account of the molecular structure and elastic properties of hair written by Dr. W. T. Astbury, remains virtually unchanged, but a number of new references are included.

The disorders and diseases of the scalp are classified according to their main presenting symptoms, a scheme which inevitably leads to some repetition, but this is less noticeable than in the third edition. There is a curious repetition, some of it word for word, of the details of the older treatments of scalp ringworm on p. 192 and 196–7. The clinical descriptions of disease are clear and vivid, and most but by no means all of the views expressed on aetiology and treatment are orthodox.

The sections on seborrhoea and baldness (Chapter VIII) and pityriasis simplex capitis (p. 159 *et seq.*) are, perhaps, the most controversial. Chapter XII on ringworm and favus has been largely rewritten by Dr. A. Rook. In general treatment has been brought fully up to date, though there is no mention of sulphonamides in the treatment of boils, nor of aureomycin in skin sepsis or calciferol for sarcoid.

The illustrations, mostly black and white photographs, are clear and well chosen. The type is legible and the binding good. This book should be of special help to general practitioners in search of a diagnosis and treatment, but it is a useful work of reference for anyone interested in dermatology, and the fourth edition will undoubtedly increase its popularity. B. C. T.

---

* *The Hair and Scalp: A Clinical Study (with a Chapter on Hirsuties).* By Agnes Savill, M.A., M.D., F.R.C.P.I. 4th edition. London: Edward Arnold & Co., 1952. Pp. 316 (including index). 59 illus. 25*s.* net.

CURRENT LITERATURE

REPORT ON A VENEREAL DISEASES SURVEY OF THE AFRICAN IN SOUTHERN RHODESIA. R. R. Wilcox. (October, 1949) Pp. 51.

This report, of far greater local than general importance, is a summary of investigations carried out from the end of April to October, 1949, in order to assess the value and possibility of some rapid form of treatment of venereal disease in S. Rhodesia. Following examination of cases and methods in several centres it became clear that as in similar areas the solution of the problem lay in more accurate diagnosis, checking of the defaulter rate, and the control of all those factors which facilitate the spread of venereal disease. The incidence of disease was impossible to assess with accuracy, but is clearly very high, and for syphilis the trial of a single shot treatment of 2·4 mega units of procaine penicillin with aluminium monostearate is advocated. A short description is given of an extravenereal syphilis of childhood, known in some districts as njovera, and in another as siakwelele. This was thought to be the same as bejel and is confused with syphilis clinically and serologically. D. I. W.

LESIONS OF THE VULVA. W. Hunter. (1950) *Med. Pr.*, 224, 613.

When dealing with lesions of the vulva it is important to exclude disease of the pelvic organs and disease of the skin elsewhere. A list is given with signs and treatment of the common diseases affecting the vulva; pruritus vulvae as such is not discussed. Kraurosis vulvae is described in detail as a retrogressive condition affecting the vestibule and vaginal orifice of an atrophic vulva, and occurring typically in post-menopausal patients. It is not precancerous and is helped by oestrogens –stilboestrol 2 to 3 mg. daily or dienoestrol 0·3 mg. three times daily.

Leukoplakia vulvae is regarded as being precancerous, and primarily affects the labia majora and prepuce of the clitoris. In the early stages there is hyperaemia of the skin, and later the skin becomes coarse and dull white in colour. Later it shrinks, fissures appear and sooner or later epitheliomata develop. It is said that in this condition hypochlorhydria and vitamin A deficiency may be present.

Other conditions mentioned are Bowen's disease, epithelioma, simple chronic vulvitis, gonorrhoea, syphilis and chancroid.

The author does not mention lichen sclerosus et atrophicans. H. R. V.

MALIGNANT MELANOMA AND THE MOLE. R. W. Rowan. (1950) *Med. Pr.*, 224, 620.

This short article describes the danger of treating pigmented moles and also methods of treating malignant melanomata.

The site distribution of 2193 cases of malignant melanoma described in the literature is analysed: 78·65% of cases arise in the skin, and 24·35% arise in the lower extremity.

Moles have become malignant after either single or repeated trauma, and commonly after application of carbon dioxide snow and caustic and after electrolysis or incomplete excision.

To prevent malignant change, all pigmented moles on sites subject to repeated trauma and any which start increasing in size should be excised widely and deeply and care taken to avoid spilling naevus cells into the wound. The moles most liable to become malignant are the slate-blue, bluish-black and black lesions slightly raised above the surface of the surrounding skin.

The only treatment possible when malignant change has occurred is wide excision, with dissection of the lymph drainage from the area. H. R. V.

HYPERVITAMINOSIS A. T. C. Wyatt, C. A. Carabello and M. E. Fletcher. (1950) *J. Amer. med. Ass.*, **144**, 304.

Hypervitaminosis A, first described by Josephs in 1944, has been recorded principally in infants and children from parental over-dosage with vitamin concentrates. The symptoms include anorexia, irritability, generalized pruritus and painful extremities. There are often repeated upper respiratory infections. The child has a yellowish pallor, the hair is sparse and coarse, the lips are dry and scaly, with angular fissures, and there is general muscular weakness and tenderness over the long bones. On x-ray examination there is irregularity of cortical structure with periosteal elevation and a single layer of subperiosteal new bone formation along the mid-portions of the shafts of the long bones. There is good recovery when vitamin A is withdrawn. A new case is reported in a girl aged 3. A. J. R.

TEMPORARY BALDNESS DUE TO COLD WAVE THIOGLYCOLATE PREPARATIONS. A. J. Reiches and C. W. Lane. (1950) *J. Amer. med. Ass.*, **144**, 305.

Ammonium thioglycolate if left on the hair too long causes splitting and fragmentation of the hair shaft. Two cases are reported which suggest that it can probably also have an irritating effect on the follicles. Both patients had been given cold waves by professional hairdressers in two different establishments. In both, between 2 and 5 days later there was hair loss over a fairly wide area, one in the frontal and the other in the occipito-parietal region. The hair regrew rapidly in both cases. A. J. R.

CHANGES IN THE TENSILE STRENGTH AND BREAKING TENSION OF HUMAN HAIR WITH CUSTOMARY COSMETIC PROCESSES OF TO-DAY. H. C. Friederich and G. Fröb. (1950) *Derm. Wschr.*, **121**, 265.

The authors, interested to know if the hair suffers injury from the modern methods of cosmetic treatment, use Schopper's method for testing the strength of fine fibres after subjecting the hairs to the various treatment processes. They are unable to detect other than negligible injury—after one treatment. Washing with alkali seems less good than without, because the hair loses lustre, and microscopically fine scaling is visible ; the hair's tensile strength is slightly increased. Cold permanent waving injures less than hot ; in both there is slight loss of tensile strength but increase of breaking tension. Bleaching with H_2O_2, and bleaching combined with permanent waving by either process has a negligible effect. Bleaching alone causes a slight decrease in breaking tension. M. S. S.

GLOMUS TUMOURS. W. Schneider and E. Eisenlohr. (1950) *Derm. Wschr.*, **121**, 225.

The writers discuss at length the literature on the glomus and on glomus tumours, and consider a case of their own worth describing for several reasons : (*a*) The multiplicity of the glomus tumours, three on one hand, all subungual. (*b*) The familial history. The patient's mother had had a glomus tumour. (*c*) The severity of the pain, which radiated at times to the heart, was made worse by cold, like her mother's, and was accompanied by constant severe headache which began with wakening in the morning. (*d*) The satisfactory response to removal of the largest tumour, the freedom from pain and headaches, and above all, the spontaneous disappearance of the smallest tumour. (*e*) The unusual histology : all the elements of the glomus were present, but it was a glomus caricatured. Of particular interest was the epithelioma-like appearance (cystic basal celled) formed by a proportion of the cells, which took the form of gyrate strands, one to six cells wide, or of small round-cell masses. The cystic appearance was produced by vacuolation of some of the cells, either several small vacuoles or a large one filling the entire sharply outlined cell. By rupture of adjacent cells blank spaces could form, obviously not of angiomatous nature because of the absence of an endothelial lining. (*f*) The metachromasia of the myxomatous stroma : the metachromasia appeared to be less surrounding vacuolated cells which had entered the stroma, and this was interpreted by the authors as due to loss of fluid by the stroma to the cell. (*g*) The absence of the elastica interna and externa. (*h*) By silver impregnation the demonstration of non-medullated nerve fibres in the mucoid connective tissue, a particularly rich network in the epithelioid modified musculature, and even very fine fibres between the epithelioid cells.

M. S. S.

CORTISONE THERAPY IN SARCOIDOSIS. L. E. Siltzbach, A. Posner and M. M. Medine. (1951) *J. Amer. med. Ass.*, **147**, 927.

A woman aged 30 with severe bilateral ocular involvement and enlarged mediastinal glands was given cortisone for 15 weeks (total dosage 13·7 grammes). There was striking improvement of visual acuity, and after one month there was only slight residual enlargement of the lymph-nodes in one hilum. The lymph-node enlargement had not recurred six months later. There was a mild exacerbation of the uveitis 3 weeks after stopping cortisone, but this was promptly controlled by cortisone eye-drops. Some corneal scarring and quiescent uveitis remained.

A. J. R.

THROMBO-EMBOLIC COMPLICATIONS ASSOCIATED WITH ACTH AND CORTISONE THERAPY. S. W. Cosgriff. (1951) *J. Amer. med. Ass.*, **147**, 924.

ACTH and cortisone increase the coagulability of the blood. Among 700 patients 40 thrombo-embolic episodes were observed in 28 patients during or shortly after treatment. These vascular

complications are more likely to occur with higher dosage. In the presence of underlying vascular disease or when there is a history of previous thrombo-embolic conditions, the employment of anticoagulant therapy should be considered. A. J. R.

TREATMENT OF CARDIOVASCULAR SYPHILIS. J. H. Stokes, C. C. Wolferth, J. Edeiken, M. S. Falk and W. T. Ford. (1951) *J. Amer. med. Ass.*, **147**, 944.

A report of 111 cases of cardiovascular syphilis treated with penicillin. Using 40,000 to 80,000 units of crystalline penicillin G 2-hourly to a total of 4,800,000 to 9,600,000 units there was little evidence of significant therapeutic shock and no unequivocal case of therapeutic paradox. Penicillin is admirably tolerated by the decompensated heart. Penicillin constitutes a notable advance in the treatment of cardiovascular syphilis, and the concomitant or subsequent use of heavy metals seems to be unnecessary. A. J. R.

EFFECT OF CORTICOTROPIN AND CORTISONE ON DEVELOPMENT AND PROGRESS OF PIGMENTED NAEVI. L. Goldman and D. F. Richfield. (1951) *J. Amer. med. Ass.*, **147**, 941.

Five of a series of 31 patients receiving prolonged ACTH or cortisone therapy developed unusual hyperpigmentation and new junctional naevi. None of the naevi showed clinical or histological evidence of malignancy. A. J. R.

CHROMATE DERMATITIS IN RAILROAD EMPLOYEES WORKING WITH DIESEL LOCOMOTIVES. J. R. Winston and E. N. Walsh. (1951) *J. Amer. med. Ass.*, **147**, 1133.

A special radiator fluid is used to prevent corrosion of the cooling system in diesel locomotives. A powder containing 24% sodium bichromate is made up into a 6% solution by adding water. Two gallons of this solution is poured into the radiator, which is then filled to capacity with water, the final radiator solution containing 0·08% bichromate. It is difficult to fill the radiator without getting the solution on the hands. Six cases of chromate dermatitis contracted in this way are reported. All showed positive patch tests to the radiator fluid and to 0·25% solution of bichromate. A. J. R.

SKIN REACTIONS TO SOME FAVOURITE PRESCRIPTIONS. P. D. C. Kinmont. (1951) *Med. Pr.*, 225, 64.

A full account is given of eruptions caused by various groups of drugs detailed under the headings sedatives, purgatives, metals and metalloids, sulphonamides, penicillin, streptomycin and local applications.

The reader is reminded that a drug must always be considered in dealing with any unusual eruption, and that patients do not usually regard patent medicines as "drugs."

The external use of such common skin sensitizers as sulphonamide, flavine, etc., should be discouraged. H. R. V.

COMMON INFECTIONS OF THE SKIN. D. I. Williams. (1951) *Med. Pr.*, 225, 170.

The skin is able to render harmless pathogenic organisms on its surface by regular desquamation, the secretion of certain fatty acids, the action of other ill-defined antibacterial agents and by the desiccating actions of the dryness of the skin and of sunlight on the skin. With bacterial invasion of the skin it is not known why these natural defences are overcome. Factors responsible are direct trauma, removal of protective fats, alteration in the pH of the skin, infection in the upper respiratory passages and changes in the general constitution of the patient.

An account is given of impetigo contagiosa, boils, sycosis barbae and intertrigo. Treatment follows generally accepted lines, and in some cases of recurrent boils and sycosis barbae the author finds intradermal injection of a stock staphylococcal vaccine combined with toxoid given at weekly intervals to be of benefit. H. R. V

PROTECTION AGAINST X-RAY AND BETA RADIATION. V. W. Archer, G. Cooper, J. G. Kroll and D. A. Cunningham. (1952) *J. Amer. med. Ass.*, **148**, 106.

The incidence of leukaemia is eight times higher in radiologists than in the rest of the medical profession, probably attributable to the fact that the customary protective measures cover only a limited proportion of the body. Lead glass fabric, which makes a durable flexible garment, offers excellent protection against x-rays and against the β radiation of atomic fission products. A. J. R.

CAN THE DERMATOLOGIST DO PSYCHOTHERAPY? Philip F. D. Seitz and James S. Gosman. (1952) *Arch. Derm. Syph., Chicago,* 66, 180.

The answer given by the authors, a dermatologist and a psychiatrist used to working together, is a qualified "yes." It depends on the dermatologist, the patient and the psychotherapy used. Illustrative examples are given of success and failure, and the Frankenstein monster which may be produced when the qualifications are not fulfilled is graphically painted. J. K.

ALOPECIAL AREATA: PREVALENCE IN JAPANESE AND PROGNOSIS AFTER REASSURANCE. Harry L. Arnold, jun. (1952) *Arch. Derm. Syph., Chicago,* 66, 191.

Alopecia areata is disproportionately prevalent among Japanese in Hawaii, where patients seem equally susceptible at all ages; 3 males are affected to 4 females. Treatment was restricted to reassuring the patient and giving an optimistic prognosis. The author considers that his results are at least as good as, if not better than, those following more orthodox treatment. J. K.

TREATMENT OF SUPERFICIAL MYCOLOGICAL INFECTIONS WITH A NEW ANTIFUNGAL AGENT. Edmond Edelson and Aaron H. Haskin. (1952) *Arch. Derm. Syph., Chicago,* 66, 244.

This is a second report on the use of 2-dimethylamino-6-(beta-dimethylaminoethoxy) benzothiazole (asterol) dihydrochloride and includes infections other than tinea capitis. The drug was used in tincture or ointment (base not stated) in 5% strength: 69% of 61 patients with tinea capitis due to *M. audouini* were cured and 19·7% improved, 68% of 53 patients suffering from moniliasis (including nail infections) were cured and 15% improved, and 8 of 11 patients with tinea versicolor were cured, the other 3 being improved. Only 1 of the 125 patients developed a sensitivity reaction. J. K.

STERNAL MARROW FINDINGS IN VARIOUS DERMATOSES. Frances Pascher, Maurice N. Richter, Harry Bellach and Florence Simm. (1952) *Arch. Derm. Syph., Chicago,* 66, 251.

Although the results are not unexpected, this article is useful as a record of negative as well as positive findings in some 22 dermatoses in 84 patients. J. K.

STANDARDIZATION OF THE WASSERMANN TEST USING PRESERVED COMPLEMENT TITRATED TO 50 PER CENT HAEMOLYSIS. P. N. Coleman. (1952) *Brit. J. vener. Dis.,* 28, 129.

A modification of the Fairbrother-Maddocks method for the Wassermann test employing 50% haemolysis as the end-point of the complement titration is described and the titration is conducted photometrically. The amboceptor titration has been investigated and a corresponding elaboration has been found to be unnecessary. The use of complement preserved by Richardson's method at a predetermined fixed titre enables standard results to be obtained irrespective of variations in the behaviour of the haemolytic system, and allows the day's tests to be begun without waiting for the working out of the complement titration. W. G. A.

SYPHILIS IN MENTAL DEFICIENCY. W. V. Macfarlane and C. B. S. Schofield. (1952) *Brit. J. vener. Dis.,* 28, 138.

A total of 1331 mental defectives were examined for syphilis and 32 (2·4%) were judged, principally on clinical and serological grounds, to have been infected. Serological evidence formed the most reliable basis upon which diagnosis could be made. Classical congenital stigmata were present in only six patients; altogether, ten were definitely proved to have the congenital variety of the disease, but in some of the remainder it must be acknowledged that syphilis might have been inherited. The authors conclude that there is no reason to suppose that syphilis accounted for mental deficiency to any real extent. W. G. A.

POSSIBLE APPLICATIONS OF ADRENOCORTICOTROPHIC HORMONE (ACTH) AND CORTISONE IN SYPHILIS. G. O. Horne. (1952) *Brit. J. vener. Dis.,* 28, 106.

The author deals with the subject in two parts. Part I is devoted to the principal physiological and pharmacological effects of ACTH and cortisone, and their application, mode of action and methods of administration are discussed. Part II comprises their possible applications in

syphilis. It is pointed out that they may contribute to the understanding of the disease as well as to its therapy. The possible effects at various stages of syphilis are outlined, and the results of experience with cortisone in ocular syphilis are briefly reviewed. In conclusion the limitations and potential dangers of the hormones are stressed. W. G. A.

NEWER METHODS IN THE DIAGNOSIS AND TREATMENT OF GRANULOMA INGUINALE. Robert B. Greenblatt and W. F. Barfield. (1952) *Brit. J. vener. Dis.*, **28**, 123.

Satisfactory methods of diagnosis of granuloma inguinale employing specific techniques of histologic study and stained tissue smears, with suggestions for obtaining good smears, are discussed. The intradermal skin test in diagnosis is reviewed. The authors conclude that, following upon the treatment of 295 patients with varied antibiotics, terramycin is the drug of choice as side effects are minimal, the need for re-treatment seldom and the total dosage is smaller. W. G. A.

CUTANEOUS RETICULOSES. A. Sezary. (1952) *Ann. Derm. Syph.*, **79**, 378.

The diagnosis of reticuloses is chiefly made by histological examination combined with the absence of any specific aetiological factor. The author distinguishes between orthoplastic reticuloses in which the cells are those seen in common inflammatory reactions, and which include such conditions as sarcoid, and metaplastic reticuloses in which abnormal cells are seen and which includes mycosis fungoides, Hodgkin's disease, etc., and in which he also places dermatofibroma of Darrier-Ferrand. The former are benign and do not respond to radiotherapy, whilst the latter temporarily respond to x-rays, but are malignant and ultimately fatal. F. F. H.

TUBERCULO-ULCEROUS AND TUBERCULO-GUMMATOUS FORMS OF GRANULOMA ANNULARE. A. Civatte. (1952) *Ann. Derm. Syph.*, **79**, 387.

Five cases are described showing a tendency to ulceration histologically and in two of them clinically. Vascular lesions were visible histologically, which might account for the degeneration. F. F. H.

A NEW ASPECT OF THE DISEASE CAUSED BY THE USE OF CANE OF PROVENCE IN THE HOUSING INDUSTRY. J. Gaté, J. Coudert and P. Therre. (1952) *Ann. Derm. Syph.*, **79**, 398.

A considerable proportion of workers handling cane developed an irritation on the points of friction from their clothes. Investigation showed that this was due to a fungus of the *Alternaria* type. Prevention consisted in stripping off the leaves and storing them in a dry place, or alternatively impregnating them with iron or zinc sulphate. F. F. H.

MALIGNANT ATROPHYING PAPULOSIS. R. Degos. (1952) *Ann. Derm. Syph.*, **79**, 410.

The author describes two cases and refers to a third one of a syndrome that starts with rose papules, the centres of which become depressed and assume a porcelain-like white colour surrounded by fine telangiectases. Subsequently an acute abdominal crisis develops with a fatal termination. At autopsy there are minute yellow spots scattered over the small intestine. The aetiology and pathogenesis of the condition is obscure. F. F. H.

HEREDITARY CONDITIONS OF CUTANEOUS ATROPHY WITH PREMATURE SENESCENCE. A. Touraine. (1952) *Ann. Derm. Syph.*, **79**, 446.

The author collects the syndromes of Rothmund, Werner, congenital poikiloderma of Thomson, atrophic myotonia of Steinert, progeria and acrogeria into what he calls an hereditary chain. Such conditions show varied attributes such as cataract, anomalies of nails, hair, and teeth, etc., accompanied by a premature sensescence which is more marked the earlier the atrophy occurs. He divides them into precocious types, either congenital or infantile, including Rothmund's syndrome, Thomson's disease and others, and late types which include Werner's syndrome and atrophic myotonia. These various conditions are connected by transitional forms which justify their being grouped under one heading. F. F. H.

NORWEGIAN SCABIES. G. C. Wells. (1952) *Brit. med. J.*, **2**, 18.

An epidemic of 67 cases of scabies, mostly atypical, occurring among patients and nursing staff of two hospitals was traced to a case of Norwegian scabies. This rare variant of ordinary

scabies is discussed with reference to the factors favouring such massive infestation and great infectivity. B. A. T.

CUTANEOUS REACTIONS TO INJECTION OF PROGESTERONE SOLUTIONS INTO THE SKIN. Vernon R. Pickles. (1952) *Brit. med. J.*, 2, 373.

Intradermal injections of progesterone solution into 30 subjects caused a complex reaction in the skin—an immediate and transitory "triple response," followed after about a week by a localized follicular eczema, which on subsiding left a pigmented patch. In different circumstances oestradiol or testosterone are known to increase skin pigmentation. The present paper provides a further example of such an effect of a sex hormone. It was shown that the initial triple response and the eczema were non-specific responses to the oily medium. B. A. T.

PSYCHIATRIC SURVEY OF A RANDOM SAMPLE OF SKIN OUT-PATIENTS. S. P. Hall-Smith and A. Norton. (1952) *Brit. med. J.*, 2, 417.

In a random sample of 150 skin out-patients, psychiatric factors were found to be significant in 78·5% of them, and the series contained a large number of persons with highly abnormal personalities. 52% of patients were of the anxious, obsessional personality type. Processes of selection are in part responsible for the high degree of psychiatric abnormality presented by out-patients. Psychiatric palliation can do much to help these patients. B. A. T.

A CASE OF CONGENITAL ICHTHYOSIFORM ERYTHRODERMIA OF BROCQ TREATED BY HYPNOSIS. A. A. Mason. (1952) *Brit. med. J.*, 2, 422.

A boy aged 16 suffered from congenital ichthyosis of considerable severity. Plastic operations were valueless. He was treated by hypnosis, and the order in which his skin would clear was suggested to him. His skin improved in this order, the final clearances of different areas varying between 50% and 100%. The inferences drawn are that either there is a hitherto unsuspected psychic factor in the aetiology of the disease, or this is a case of a congenital organic condition being affected by a psychological process. B. A. T.

FROSTBITE: AN ANALYSIS OF SEVENTY-ONE CASES. E. A. Edwards and R. W. Leeper. (1952) *J. Amer. med. Ass.*, **149**, 1199.

This report is based on 71 cases of frostbite encountered in Korea in the winter 1950–1951. The factors which predispose to frostbite are the existence of chronic vasospasm or hyperidrosis, previous cold injury, wounding, and possibly tobacco smoking. The clinical picture of frostbite is fully described, and it is emphasized that the superficial necrosis is always more extensive than the underlying gangrene. The extent of the necrosis depends on the duration of freezing after the initial symptoms. The indications for sympathicolytic drugs and sympathectomy are discussed. A. J. R.

GENITO-URINARY LESIONS IN LEPROSY, WITH SPECIAL REFERENCE TO THE PROBLEM OF ATROPHY OF THE TESTES. H. Grabstald and L. L. Swan. (1952) *J. Amer. med. Ass.*, **149**, 1287.

The authors examined 179 men with leprosy and found atrophy of the testes in 28% and gynaecomastia in 19%. Histological study of the testes of 20 subjects showed a leprous orchitis with infiltration of vessel walls and adjacent tissues by *Mycobacterium leprae*, clumping of interstitial cells and atrophy of seminiferous tubules proceding eventually to complete fibrosis. A. J. R.

APLASTIC ANEMIA ASSOCIATED WITH ADMINISTRATION OF CHLORAMPHENICOL. M. M. Hargraves, S. D. Mills and F. J. Heck. (1952) *J. Amer. med. Ass.*, **149**, 1293.

CHLORAMPHENICOL AND APLASTIC ANEMIA. J. J. Rheingold and C. L. Spurling. (1952) *J. Amer. med. Ass.*, **149**, 1301.

The first article reports 10 cases of aplastic anemia attributable to chloramphenicol. There appear to be three patterns of bone-marrow response to this antibiotic. Some cases appear to depend on a sensitivity mechanism, the bone-marrow failure being precipitated by a second course of chloramphenicol. In 2 cases the second course consisted of as little as 4 capsules. In other cases the first course precipitated acute aplasia of the marrow, and in a third group gradual suppression of the marrow followed the prolonged administration of small doses. No treatment

seemed to be of value. Neither ACTH nor vitamin B_{12} had any obvious effect. Death in the fatal cases was due to uncontrollable haemorrhage.

The second article records 5 more fatal cases. A. J. R.

CUTANEOUS ALLERGY FROM LOCAL CONTACT WITH ISONICOTINIC ACID HYDRAZID. J. W. Jordon. (1952) *J. Amer. med. Ass.*, **149**, 1316.

A short case-report. The patient was a pharmaceutical chemist. A. J. R.

A STUDY OF RUBBER ADHESIVES IN SHOES AS THE CAUSE OF DERMATITIS OF THE FEET. I. H. Blank and O. G. Miller. (1952) *J. Amer. med. Ass.*, **149**, 1371.

Twenty-four patients, all of them women with dermatitis considered to be caused by sensitivity to shoe materials, were carefully investigated. Patch tests to portions of the shoes were positive in 20, and in 3 cases no material from the suspected shoes could be obtained. In one case the tests were negative. In the majority of cases positive reactions were provoked by the combined cloth linings, which were held together by rubber adhesive. A study of patch test reactions to a number of accelerators and antioxidants showed that the antioxidant, monobenzyl ether of hydroquinone, used in the adhesive was most commonly responsible. Some of the patients were, however, specifically sensitive to other rubber antioxidants and accelerators. A. J. R.

HORMONAL MANAGEMENT OF HEREDITARY HEMORRHAGIC TELANGIECTASIA. H. J. Koch, G. C. Escher and J. S. Lewis. (1952) *J. Amer. med. Ass.*, **149**, 1376.

On account of the apparent connection between the menstrual cycle and recurrent epistaxis in a patient with hereditary haemorrhagic telangiectasia ethinyl oestradiol therapy was employed in 5 cases. In all patients the incidence and severity of epistaxes decreased and the skin lesions blanched and diminished in size. Oestrogen administration must be maintained to prevent relapses. It is uncertain whether oestrogen acts directly on the vascular lesions, or merely protects the telangiectases from trauma by restoring the nasal mucous membrane to its normal texture. In the 2 males methyltestosterone given simultaneously prevented feminization. Sodium and water retention were controlled by a low sodium diet and diuretics. A. J. R.

PRESENT ROLE OF ZINC PEROXIDE IN TREATMENT OF SURGICAL INFECTIONS. F. L. Meleney. (1952) *J. Amer. med. Ass.*, **149**, 1449.

Sulphonamides and antibiotics have not entirely supplanted zinc peroxide in treatment of surgical infections. It is particularly useful in undermining burrowing ulcers, in synergistic gangrene after excision and in decubitus ulcers, in diabetic gangrene, in foul-smelling lesions of the mouth and neck, in radiation burns and in certain other conditions. Zinc peroxide is most active in a watery suspension, but can be used in a carbowax base. A. J. R.

TOPICAL CHLORAMPHENICOL (CHLOROMYCETIN) THERAPY OF PYOGENIC DERMATOSES. E. R. Trice and J. C. Shafer. (1952) *J. Amer. med. Ass.*, **149**, 1469.

Chloramphenicol cream (2%) was used in 100 superficial and deep pyogenic dermatoses. Eighty six were followed up. The superficial infections responded well, the majority clearing in 3 to 10 days, an efficacy equal to that of aureomycin and bacitracin. For deep pyodermas the chloramphenicol cream was no more effective than other antiseptic preparations. There was no proved case of hypersensitivity. A. J. R.

ENZYME DEBRIDEMENT OF INDOLENT INFECTED CUTANEOUS ULCERS. J. F. Madden and H. G. Ravits. (1952) *J. Amer. med Ass.*, **149**, 1616.

The enzymes streptokinase and streptodornase ("varidase") bring about lysis and digestion of fibrin and desoxyribose nucleoprotein, eliminating pus and debris and facilitating the formation of healthy granulation tissue. "Varidase" and purified crystalline trypsin were used in a series of cases of indolent infected cutaneous ulcers, chiefly of hypostatic origin, and were considered to be useful adjuvants. A. J. R.

PERIARTERITIS NODOSA. L. R. Cole. (1952) *J. Amer. med. Ass.*, **149**, 1649.

Recent reviews show that a diagnosis of periarteritis nodosa is established antemortem in only 12% of cases. Krupp in 1943 observed a type of urinary sediment which he considered to be characteristic of acute disseminated lupus erythematosus and periarteritis nodosa—the presence in a single specimen of urine of red blood cells, red cell cases, oval fat bodies, fatty and waxy

casts and frequently also broad casts. A case of periarteritis nodosa is recorded in which this type of urinary sediment was present, and the author believes that although it is probably not pathognomonic it is of considerable assistance in diagnosis. A. J. R.

PRURITUS VULVAE AS SEEN IN DERMATOLOGICAL PRACTICE. F. W. Lynch. (1952) *J. Amer. med. Ass.*, **150**, 14.

Reviewing the recent literature on pruritus vulvae the author points out that many published reports fail to give an accurate impression of the problem as it is encountered by the dermatologist. He reports a personal series of 112 patients in whom pruritus vulvae was the primary complaint. There were no examples of lichen planus or seborrhoeic dermatitis, and only once was contact dermatitis a primary cause of the pruritus though it was often a complication. The coexistence of a number of contributory factors is frequent and it is difficult to assess their relative importance. The sequence of involvement of vulva and perianal regions and the nature of the lesions were correlated with age of onset and with atopic, infective and psychological factors. In the 15 patients with localized periclitoral involvement psychological factors were particularly evident. Menstrual irregularities were common, but the significance of endocrine influences is doubtful. Disturbances in sugar metabolism were present in at least 15%, and were usually associated with redness, swelling and infection. Vaginitis and discharge or other pelvic disease was present in 40%.

Treatment is briefly discussed. The author advocates sedation, control of contributory organic factors, intelligent topical therapy, limited use of x-ray therapy and "family doctor" type of superficial psychotherapy. He condemns injection, vulvectomy and neurosurgical procedures. A. J. R.

SUCCESSFUL TREATMENT OF HYPERHIDROSIS WITH METHOBARBITAL. W. G. Scanlon. (1952) *J. Amer. med. Ass.*, **150**, 28.

Mephobarbital is believed to act on the diencephalon. In effective doses it produces less narcosis in anxiety states than other barbiturates and does not produce the mydriasis, dry mouth and constipation often encountered with Banthine. Two cases of severe hyperidrosis were controlled by 0·2 to 0·4 grammes of mephobarbital daily, and the author recommends this drug, particularly for hyperidrosis of emotional origin. A. J. R.

INHIBITION OF TUBERCULIN REACTION BY LOCAL INJECTION OF COMPOUND F. L. Goldman, R. H. Preston, E. Rockwell and J. Baskett. (1952) *J. Amer. med. Ass.*, **150**, 30.

Tuberculin reactions and tuberculin type inflammatory reactions can be inhibited to a significant degree by the local injection of Compound F. A. J. R.

SUCCESSFUL TREATMENT OF ACTINOMYCOSIS WITH "STILBAMIDINE." J. M. Miller, F. Howard, P. H. Long and E. B. Schoenbach. (1952) *J. Amer. med. Ass.*, **150**, 35.

A case of actinomycosis that had failed to respond to penicillin or sulphadiazine, which are usually considered the treatments of choice, was treated with Stilbamidine with a prompt and ultimately complete response. Stilbamidine was tried because of the good results which the authors had obtained with Stilbamidine intravenously and Propamidine locally in blastomycosis. A. J. R.

DIFFERENCE IN REDNESS BETWEEN THE FOURTH CERVICAL AND THE THORACIC SEGMENTS ON THE ANTERIOR SURFACE OF THE TRUNK FOLLOWING IRRITATION WITH MUSTARD OIL. J. Adams-Ray. (1952) *Acta derm.-venereol., Stockh.*, **32**, 10.

Irritation of the skin of the chest with mustard oil produces in the normal skin stronger and more extensive erythema in the 4th cervical segment than in the subjacent second thoracic and caudal segment. Photometric measurement was made. Newborn children exhibit the same phenomenon ; which may be due to increased sympathetic tone in the paler areas due to stronger afferent visceral impulses. G. A. H.

BACTERIOLOGICAL AND IMMUNOLOGICAL STUDIES IN ATOPIC DERMATITIS. A. Rostenberg, E. E. Vicher and M. J. Brunner. (1952) *Acta derm.-venereol., Stockh.*, **32**, 1.

No evidence was produced for or against a hypothesis that atopic dermatitis is caused by bacterial sensitization. Experiments included cultures from skin and mucous membranes and the use of ground and unground vaccines of organisms cultured. G. A. H.

HERPES ZOSTER FOLLOWING BILATERAL SUPRANUCLEAR SYMPATHICOTOMY. B. I. Svendsen. (1952) *Acta derm.-venereol., Stockh.*, **32**, 20.

Bilateral supranuclear sympathectomy in a 34-year-old labourer interrupted the function of the 2nd and 3rd thoracic spinal nerves.

After 8 years a unilateral right-sided herpes zoster developed over the areas innervated by the 6th cervical and 1st and 2nd thoracic spinal nerves, with bilateral marked hyperaesthesia and nodal enlargement over the areas innervated by spinal ganglia above and below the nerves affected by the operation. A relationship between the operation and the herpes is suggested because of the bilateral symptoms and site of the lesion. G. A. H.

PODOPHYLLIN TREATMENT OF SKIN CARCINOMAS. L.-G. Larsson. (1952) *Acta derm.-venereol., Stockh.*, **32**, 56.

Local application of podophyllin is suitable in (1) precancerous dermatoses ; (2) intraepidermal basal-cell carcinomas ; (3) other superficial extensive forms of basal-cell carcinomas not more than 2 mm. thick ; (4) superficial basal-cell carcinomas in areas already treated with radium or x-ray. Efficient follow-up will be required to determine the final end results.

20–25% of podophyllin was used in ointment bases. Within 24–48 hours of application hyperaemia occurred, followed by ulceration and sloughing off of the tumour over subsequent days. After 5–6 days the area was covered with a thin layer of epithelium. G. A. H.

INOCULATION LUPUS AFTER BCG VACCINATION. O. Gilje. (1952) *Acta derm.-venereol., Stockh.*, **32**, 51.

Lupus developed at the site of BCG vaccination in a girl of 13 who was revaccinated 1 year after the first vaccination. G. A. H.

WATER-BORNE TUBERCULOUS AND SIMILAR INFECTIONS OF THE SKIN IN SWIMMING-POOLS. S. Hellerstrom. (1952) *Acta derm.-venereol., Stockh.*, **32**, 449.

Water-borne infections of the skin acquired in swimming-baths are divided clinically and bacteriologically into two types : inoculation lupus of the bridge of the nose and non-characteristic crusted sores on the elbows. The latter type is due probably to a mycobacterium practically indistinguishable from Koch's bacillus and possibly analogous to *Mycobacterium aquarium*.

G. A. H.

IS THERE A POSSIBILITY OF TUBERCULOUS INFECTION THROUGH INJURIES SUSTAINED IN SWIMMING-POOLS ? C. Bruck. (1952) *Acta derm.-venereol., Stockh.*, **32**, 443.

A case of proved inoculation lupus in a man injuring himself in a swimming-bath with a positive T.B. culture and positive inoculation guinea-pig tuberculosis. After discussing other cases the author considers that some are due to Koch's bacillus and others to another mycobacterium.

G. A. H.

SOME INVESTIGATIONS ON HYPERSENSITIVENESS TO BICHROMATE IN CEMENT WORKERS. J. K. Engebrigtsen. (1952) *Acta derm.-venereol., Stockh.*, **32**, 462.

The chromium content of cement in a factory of 400 workers was 0·002% to 0·02%.

Patch tests on 8 cases of cement eczema with $\frac{1}{2}$% potassium bichromate were positive in 7 cases and positive to cement in 4 cases. 10 control eczema cases showed no response. Patch tests with washed-out cement (divested of chromium) showed no reaction on the four patients who gave reactions to ordinary cement. Cement eczema depends upon a combination of a toxic and allergic action ; the allergen may be identical with the demonstrable water-soluble chromates found in all cement. G. A. H.

CLINICAL AND HISTOLOGICAL PICTURE OF ACRODERMATITIS CONTINUA. F. Kogoz. (1951) *Arch. Derm. Syph., Berl.*, **193**, 29.

The author states that he first described the corneal or subcorneal " spongiform " pustule in acrodermatitis continua. He would have liked to maintain that this was a definite diagnostic histological criterion. However, although in the present paper he records the " spongiform " pustule in a further case of acrodermatitis continua, he also found it in pustular psoriasis. Impetigo herpetiformis, Reiter's disease and keratoderma blenorrhagicum may show similar features.

M. F.